REMARKS

Summary of the telephonic interview of May 14, 2007

The undersigned applicants' representative acknowledges with gratitude the examiner's patient and professional explanation during the telephonic interview of May 14, 2007, of the reasons for maintaining the rejection of the claims under 35 U.S.C. 103(a).

Participating in the telephonic interview were the examiner and the applicants' representatives, Dr. Charles C. P. Rories and Dr. Thomas A. Cawley (the undersigned).

In "walking through" the basis for rejection, the examiner explained that he understood that the tetravalent Abs of the claimed invention form spontaneously in a preparation of the CH2 domain deleted antibodies, and that he considered that normal purification methods such as those described in the cited Thorpe et al. and Kashmiri et al. references would result in purification of the tetravalent antibodies of the claimed invention. The examiner further stated that he considered the rejection to be proper in view of MPEP 2145(II) and the decision of Ex Parte Obiaya, 227 USPQ 58, 60 (BPAI 1985), which held that the discovery of an additional advantage in doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention.

The applicants' representatives stated that at the time the invention was made one of ordinary skill in the art did not know that the CH2 domain deleted antibodies spontaneously formed the dimeric, tetravalent antibodies of the claimed invention, and so would not have selected purification procedures that would result in purifying the dimeric, tetravalent antibodies of the claimed invention from the known monomeric, divalent antibodies. The applicants' representatives also stated that the purified dimeric, tetravalent antibodies of the claimed invention are qualitatively different from a mixture of divalent and tetravalent antibodies that would be obtained using normal purification methods of the prior art, because the tetravalent antibodies bind the target antigen with a significantly higher apparent binding affinity than the divalent antibodies. As additional evidence of non-obviousness, the applicants' representatives further noted that although Gillies et al. described performing experiments in an attempt to identify the reason why a preparation of the CH2 domain deleted antibodies binds to the target antigen with a higher apparent binding affinity, they did not discover or even consider that the

higher apparent binding affinity was due to the presence in their antibody preparation of the spontaneously formed dimeric, tetravalent antibodies.

The examiner stated that the applicants' representatives' arguments that the purified tetravalent antibodies of the claimed invention were not obvious to one of ordinary skill in the art at the time the invention was made would be given consideration, and suggested that the claims be amended to specify that the substantially purified tetravalent Abs of the claimed invention are purified to greater than 98% homogeneity, as described on page 53 of the application.

Preliminary Remarks

Claims 20, 29, 80, 85, 94, 96, 98 and 100 are amended, and claims 93, 95, 97, 99, and 101 are canceled.

Independent claims 20, 29, 80, and 85 are amended to specify that the substantially purified dimeric, tetravalent antibodies of the claimed invention are purified from monomeric, divalent, C_H2 domain-deleted antibodies that bind specifically to TAG-72 as described in the specification, *e.g.*, in Examples 4 and 5 on pages 51-53, which describes purifying the dimeric, tetravalent antibodies of the claimed invention from monomeric, divalent, C_H2 domain-deleted anti-TAG-72 antibodies.

Claims 94, 96, 98 and 100 are amended to specify that the substantially purified dimeric, tetravalent antibodies of the claimed invention are purified to greater than 98% homogeneity, as described in the specification, *e.g.*, on page 53, line 8.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Patentability Remarks

35 U.S.C. §103(a)

Claims 20, 29, 38-40, 62-63, 75-80, and 84-101 remain rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Gillies et al. (1990, Human Antibodies and Hybridomas, 1(1):47-54), as evidenced by the specification, in view of Kashmiri et al. (5/11/2000, WO

00/26394), Anderson et al. (U.S. Patent No. 6,348,581 B1) and Thorpe et al. (U.S. Patent No. 6,342,219 B1). Please note that rejected claims 93, 95, 97, 99, and 101 are canceled.

Independent claims 20, 29, 80, and 85 are amended to specify that the substantially purified dimeric, tetravalent antibodies of the claimed invention are purified from monomeric, divalent, C_H2 domain-deleted antibodies that bind specifically to TAG-72, as discussed above.

In the official action dated November 20, 2006, the examiner has maintained the rejection of the claims under 35 U.S.C. §103(a) as being obvious in view of Gillies et al., as evidenced by the specification, in view of Kashmiri et al., Anderson et al., and Thorpe et al. The examiner argues that the rejection is appropriate because dimeric, tetravalent (H_4L_4) CH2 domain-deleted anti-TAG72 antibodies of the claimed invention would form spontaneously in a composition of chimeric CH2 domain-deleted anti-TAG72 antibodies prepared according to the teachings of Gillies et al. and Anderson et al., and normal purification methods such as those described in the cited Thorpe et al. and Kashmiri et al. references would result in purification of the tetravalent antibodies of the claimed invention. The examiner further argues that advantages obtained by making or using the substantially purified dimeric, tetravalent antibodies of the claimed invention are considered to "flow naturally from following the suggestion of the prior art" to prepare the substantially purified dimeric, tetravalent antibodies of the claimed invention, and cites the decision of Ex Parte Obiaya, 227 USPQ 58, 60 (BPAI 1985), which held that the discovery of an additional advantage in doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention.

The applicants submit that the combination of the Gillies et al., Kashmiri et al., Anderson et al., and Thorpe et al., references does not describe or suggest making or using the substantially purified dimeric, tetravalent anti-TAG72 antibodies of the claimed invention which are purified from monomeric, divalent, C_H2 domain-deleted anti-TAG72 antibodies, as specified in the presently amended claims. Furthermore, neither the combination of the Gillies et al., Kashmiri et al., Anderson et al., and Thorpe et al., nor generally available knowledge would have provided one of ordinary skill in the art at the time the invention was made with a suggestion or motivation to combine the teachings of the cited references to prepare the purified dimeric, tetravalent CH2 domain-deleted anti-TAG72 antibodies of the claimed invention. At the time

the invention was made, one of ordinary skill in the art did not know that dimeric, tetravalent CH2 domain-deleted anti-TAG72 antibodies of the claimed invention even existed, and their purification would not have been achieved by standard antibody purification methods. Accordingly, at the time the invention was made, one of ordinary skill in the art would have had no reasonable expectation that routine antibody purification methods would successfully purify the dimeric, tetravalent CH2 domain-deleted anti-TAG72 antibodies of the claimed invention from monomeric, divalent, C_H2 domain-deleted antibodies that bind specifically to TAG-72.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re* Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re* Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re* Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See* M.P.E.P. § 2142.

Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re* Hedges, 783 F.2d 1038, 228 USPQ 686 (Fed. Cir. 1986). *See* M.P.E.P. § 2145(X)(D)(3). It is improper to combine references where the references teach away from their combination. *In re* Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). *See* M.P.E.P. § 2145(X)(D)(2).

A. No teaching or suggestion of all claim limitations

At the time the invention was made, the prior art did not teach or suggest, and persons of ordinary skill in the art did not know or suspect, that dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention existed or could be formed. The cited prior art references and neither described nor suggested making or using the substantially purified dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention, which are purified from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies as specified in the present claims.

B. No suggestion or motivation to modify or combine the teachings of the cited references to obtain the claimed invention

The claims are amended to specify that the dimeric, tetravalent CH2 domain-deleted anti-TAG72 antibodies of the claimed invention are purified from monomeric, divalent, C_H2 domain-deleted antibodies that bind specifically to TAG-72. Prior to the applicant's discovery and purification of dimeric, tetravalent, CH2 domain-deleted anti-TAG72 antibodies, it was simply not known that such dimeric antibody complexes existed, and normal, standard methods of antibody purification used at the time the invention was made would not have resulted in purification of the dimeric, tetravalent CH2 domain-deleted anti-TAG72 antibodies of the claimed invention from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies

Gillies *et al.* describe a method for preparing chimeric, CH2 domain-deleted anti-TAG-72 antibodies, and teach that their method results in the formation of 60 kDa HL "half-molecules" that contain one light chain and one ΔCH2 heavy chain, and 120 kDa H_2L_2 molecules consisting of two 60 kDa HL "half-molecules." The reference describes analyzing the CH2 domain-deleted antibody molecules produced by their method with non-denaturing HPLC size exclusion chromatography, and teach that the 60 kDa HL antibodies and the 120 kDa H_2L_2 molecules "migrate as one peak" during non-denaturing size exclusion chromatography. Although Gillies et al. performed HPLC size exclusion chromatography on the mixture of antibody molecules produced by their method, they did not describe observing the dimeric

(H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention, or even suggest that such dimeric (H_4L_4, 240 kDa) CH2 domain-deleted antibodies might exist.

Kashmiri et al. and Thorpe et al. and the generally available knowledge regarding standard methods for purifying antibodies, in combination with the teachings of the Gillies et al., would not have provided one of ordinary skill in the art at the time the invention was made with a suggestion or motivation to combine the teachings of the cited references to obtain the substantially purified dimeric, tetravalent, CH2 domain-deleted anti-TAG72 antibodies of the claimed invention. Kashmiri et al. and Thorpe et al. provide a general teaching that antibodies can be purified using known methods. In particular, Kashmiri et al. teaches using "standard procedures" for antibody purification, "including ammonium sulfate precipitation, affinity columns, column chromatography, and gel electrophoresis" (*see* page 17, lines 20-24); and Thorpe et al. teaches that the antibodies can be purified "using filtration, centrifugation, and various chromatographic methods such as HPLC or affinity chromatography" that are "well known to those of skill in the art." (col. 61, lines 10-19). The methods identified by the Kashmiri et al. and Thorpe et al. cited references as "standard" techniques, *e.g.*, filtration and ammonium sulfate precipitation, and most commonly used forms of standard and high pressure liquid chromatography (HPLC), such as ion exchange, affinity, and reverse phase chromatography, generally would not result in separation of dimeric (240 kDa), tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the present invention from monomeric (120 kDa), divalent, CH2 domain-deleted anti-TAG-72 antibodies present in a mixture. As shown in the present application, the dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies of the present invention can be purified from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies present in an antibody mixture by size exclusion chromatography (SEC) which uses a SEC medium capable of separating the 240 kDa, dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies of the present invention from the 120 kDa, monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies. However, as discussed above, Gillies et al. described purifying CH2 domain-deleted anti-TAG-72 antibodies to greater than 90% homogeneity by a purification protocol comprising protein A chromatography followed by immunoaffinity chromatography, and then performing HPLC size exclusion chromatography on the antibody mixture, without observing the dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies

of the present invention. As shown by Gillies et al., one of ordinary skill in the art who did not know of the existence of the dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies of the present invention would not normally select a SEC medium that separates high molecular weight dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies of the present invention from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies that are present in an antibody mixture, and so would not achieve purification of the high molecular weight dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies of the present invention from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies. Neither the cited combination of references nor the generally available knowledge would have provided a suggestion or motivation to one of ordinary skill in the art at the time the invention was made to purify the dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the present invention from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies.

C. There was no reasonable expectation that the use of known, standard antibody purification methods would result in successful, substantial purification of dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention from monomeric, divalent CH2 domain-deleted anti-TAG-72 antibodies.

Gillies et al. reported what they describe as the "surprising" and "unexpected" finding that the apparent antigen binding activity of the CH2 domain-deleted antibodies produced by their method is significantly higher than that of the corresponding wild-type antibodies (*e.g., see* page 49, right column, and page 53, left column). Gillies et al. describe experiments they performed in an unsuccessful effort to determine the structural basis for the observed increased antigen binding activity of the CH2 domain-deleted antibodies produced by their method (*see* pages 50-52 and page 53, right column). As discussed above, Gillies et al. described using HPLC SEC to analyze the CH2 domain-deleted anti-TAG-72 antibodies produced by their method, but did not describe observing dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the present invention, **even though they were actively seeking a structural basis for the high antigen binding affinities that they observed**. The failure of Gillies et al. to observe and purify dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies having

molecular weight of 240 kDa of the present invention, even when they were actively looking for antibody structures that might explain the high antigen binding affinities they observed, is strong evidence that identification and purification of dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the present invention would not have been obvious at the time the invention was made. Without knowing of their existence, one of ordinary skill in the art would not have detected the dimeric, tetravalent CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention, and successfully purified them from the known monomeric, divalent, CH2 domain-deleted anti-TAG-72 antibodies, just as Gillies et al. failed to do so.

For the reasons discussed above, the claimed invention therefore would not have been obvious to one of ordinary skill in the art at the time the invention was made in view of Gillies et al. (1990), as evidenced by the specification, and further in view of Kashmiri et al., Anderson et al., and Thorpe et al., and withdrawal of the rejection of claims 20, 29, 38-40, 62-63, 75-80, 84-92, 94, 96, 98 and 100 under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

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